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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,413	06/23/2006	Kenya Shitara	Q107168	1999

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EXAMINER	
WEN, SHARON X	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
04/15/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/581,413	SHITARA ET AL.	
	Examiner	Art Unit	
	SHARON WEN	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5,6 and 27-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6 and 27-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment, filed 01/22/2010, has been entered.

Claims 1-4, 7-26 and 42-46 have been canceled.

Claims 5 and 27 have been amended.

Claims 5-6 and 27-41 are and currently under examination as they read on a method for treating a CCR4-expressing tumor comprising administering a recombinant antibody that specifically binds chemokine receptor 4 (CCR4).

It is noted that the species of "agent" recited in claim 5 that are currently under examination are G-CSF (elected by Applicant in the reply filed on 08/28/2008) and M-CSF, IL-2, vincristine, cyclophosphamide, etoposide and methotrexate (extended by Examiner in the Office Actions, mailed 12/11/2008 and 07/22/2009).

2. This Action will be in response to Applicant's Arguments/Remarks, filed 01/22/2010.

The rejections of record can be found in the previous Office Actions, mailed 10/17/2007, 12/11/2008 and 07/22/2009.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 5-6 and 27-41 stand rejected under 35 U.S.C. 103(a) as being obvious over Shitara et al. (US 2003/0175273 A1, reference of record) in view of Taub (U.S. Patent 6,762,174 B1, reference of record).

Applicant's argument has been considered in full but has not been found convincing for reasons of record. The rejection of record can be located in the previous Office Action, mailed 07/22/2009, and is reiterated below for Applicant's convenience.

> Shitara et al. taught a method for treating CCR4-related cancer such as leukemia or lymphoma, which read on hematopoietic organ tumor (given that *hematopoiesis* means the formation of blood cellular components), in which the cancer cells express CCR4 comprising administering an anti-CCR4 antibody that has antibody-dependent cell-mediated cytotoxicity (ADCC) function (see paragraphs [0019]-[0020], [0030]-[0040], [0070]-[0074], [0230], [0233], [0236] and claims 41-45). The prior art antibody appears to be the same or nearly the same antibody as the instant application with identical CDRs (see paragraphs [0049]-[0050] and SEQ ID NOs: 1-3 and 5-7). In addition, the reference taught the antibody which is a human chimeric antibody or a human CDR-grafted antibody (see abstracted and paragraph [0310]) which read on a recombinant antibody. The prior art also taught that the monoclonal antibody is produced by hybridoma KM2160 (see paragraph [0255]-[0258]). Furthermore, the prior art antibody binds to the same CCR4 epitope as recited in the present claims (see paragraphs [0033]-[0036]. Given the same or nearly the same antibody (i.e., having the same CDRs and produced by the same hybridoma), the prior art antibody would necessarily not have an activity of inhibiting binding of TARC or MDC as a CCR4 ligand to CCR4. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.,* 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).
>
> Shitara et al. differs from the present claims in that it did not specifically teach the antibody used in the claimed method which is not conjugated to at least one agent. However, Shitara et al. taught a medicament comprising the antibody as the active ingredient and that the antibody can be administered alone or in a pharmaceutical formulation (see paragraphs [0070]-[0071] and [0238]). Given that the prior art antibody has ADCC activity, one of ordinary skill in the art would have readily recognized that the antibody does not need to be conjugated to an agent to exert its therapeutic effect (i.e., inducing cytotoxic effect on CCR4-expressing cancer cells).
>
> Although it is not necessarily to conjugate the antibody, one of ordinary skill would be reasonably expected to include an unconjugated therapeutic agent in the medicament comprising the anti-CCR4 antibody for treating cancer wherein the therapeutic agent can be any well-known chemotherapeutic agents such as

vincristine, cyclophosphamide, etoposide and methotrexate as evidenced by Taub (see entire document, in particular, see column 6, second paragraph). In particular, Taub taught that combining a Formula I compound and a well-known anti-cancer agent such as vincristine, cyclophosphamide, etoposide or methotrexate would produce synergism in treating cancer (see column 6, lines 9-26). Therefore, one of ordinary skill in the art, upon reading Taub, would have been motivated to include a therapeutic agent such as vincristine, cyclophosphamide, etoposide or methotrexate in the medicament comprising the anti-CCR4 antibody as the active agent for treating cancer for the advantage of synergism (e.g., decreasing dose-limiting side effects).

Given that Shitara et al. taught that the anti-CCR4 antibody has ADCC activity and can be administered alone and the teaching by Taub in that well-known chemotherapeutic agents such as vincristine, cyclophosphamide, etoposide or methotrexate, when combined with an anti-cancer compound, would yield synergism in treating cancer, it would have been obvious to one of ordinary skill in the art to combine the anti-CCR4 antibody with a chemotherapeutic agent such as vincristine, cyclophosphamide, etoposide or methotrexate that is not conjugated to the antibody because the antibody by itself has ADCC activity.

One of ordinary skill in the art would have been equally motivated to include a cytokine, such as G-CSF, M-CSF or IL-2, in the medicament comprising anti-CCR4 antibody for treating CCR4-related cancer because these cytokines are known to activate immune cells (see Shitara et al., paragraph [0163]). Therefore, the ordinary skilled artisan would have been motivated to use these as the additional agent in the medicament to boost the patient's immunity against cancer. It would have been equally obvious to one of ordinary skill in the art not to conjugate the cytokine to the antibody because the antibody has ADCC activity by itself, thus making conjugation unnecessary.

Given the above discussion, the invention, as a whole, was *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant argues that the claimed method is not obvious because the treatment of CCR4-expressing tumor in a patient comprising administering to the patient a CCR4 specific antibody and at least one agent selected from the group consisting of G-CSF, M-CSF, interferon-alpha, IL-2, IL-15, vincristine, cyclophosphamide, etoposide and methotrexate wherein the agent is not conjugated to the antibody, **exhibit synergy with regard to the treatment of CCR4-expressing tumors *in vivo*, and that such synergy would have been unexpected to those ordinary skill in the art**. Applicant relies on the data depicted in Figures 1-7 and Table 7 to show the unexpected superior efficacy of the combination of anti-CCR4 antibody with each agent and asserts that the

efficacy of administering anti-CCR4 antibody and the agent, unconjugated, is greater than the sum of each of the effects taken separately, and thus is synergistic. Applicant further argues that synergism in combination therapies containing therapeutic antibodies and IL-2, GM-CSF is unpredictable therefore one of ordinary skill in the art could not have predicted or expected the presently claimed method to possess the beneficial properties it does. Lastly, Applicant notes that the synergy referred to by Taub et al. is made in the narrow context of combination therapies containing compounds encompassed by formula I therein, not antibodies, therefore, Taub et al. failed to suggest or incite any expectation that any giving combination of anti-cancer therapies would exhibit synergy, much less that combination therapies specifically containing therapeutic antibodies would be expected to exhibit synergy.

In response to Applicant's argument on unexpected results of synergy from the combined therapy of the anti-CCR4 antibody and each agent and the data shown in the instant specification which Applicant relies on for evidence of synergy, the following is noted:

The evidence on synergy between anti-CCR4 antibody/IL-2 shown in Figure 1 and Example 1 is not convincing because the evidence shows only *in vitro* data. The claimed method is drawn to treating CCR4-expressing tumor in a patient, i.e., *in vivo* and Applicant's argument is also drawn to synergy *in vivo* as well (see, e.g., second paragraph on page 9 of Applicant's Remarks, filed 01/22/2010). As such, the evidence is not commensurate in scope with claimed invention and thus insufficient to overcome the *prima facie* obviousness rejection of record. See MPEP § 716.02(d).

The evidence on synergy between anti-CCR4 antibody/vincristine (VCR) shown in Figure 2, Example 2 has not been found convincing because the difference between Group A (negative control) and Group D (anti-CCR4 antibody + VCR) is not significantly greater than the combined difference between Group A and Group B (anti-CCR4 antibody alone) and Group A and Group C (VCR alone). Furthermore, it is noted that the dosages of anti-CCR4 antibody and VCR in the combined therapy group (Group D) are the same as that alone (Groups B and C). The additive effect of Group D could simply be due to an increase in the total amount of components administered (antibody

and VCR). In order to show synergy, it would require a showing of a greater than additive effect. Here, the additive effect of combined therapy is not greater than each component alone. Therefore, the evidence is not sufficient to overcome the *prima facie* case of obviousness set forth in the rejection of record.

Similarly, the evidence on synergy between anti-CCR4 antibody/cyclophosphamide (CPA) shown in Figure 3 and Example 3 was not found convincing for the same reason as that above. The difference between Group A (negative control) and Group D (anti-CCR4 antibody + CPA) is not greater than the combined difference between Group A and Group B (anti-CCR4 antibody alone) and Group A and Group C (CPA alone). The additive effect was not greater than that of each component alone, thus the results are not significant or sufficient to overcome the *prima facie* case of obviousness set forth in the rejection of record.

The evidence on synergy between anti-CCR4 antibody/etoposide (VP16) shown in Figure 4, Example 4 has not been found convincing for the following reason. Although the difference between Group A (negative control) and Group D (combined therapy) is greater than the sum of the differences between Group A and Group B (anti-CCR4 antibody alone) and Group A and Group C (VP16 alone), given that the dosages of anti-CCR4 antibody and VP16 in the combined therapy group (Group D) are the same as each component alone (Groups B and C), it is not clear the additive effect is a result of true synergy or due to an increase in the total amount of components administered. Furthermore, the prior art by Taub et al. taught that etoposide was a well-known anti-cancer agent that is known to produce synergistic effect in anti-cancer therapy at the time of the invention was made. Therefore, it would have been obvious to one of ordinary skill in the art to combine etoposide with anti-CCR4 antibody for the same purpose of treating cancer with no change in their respective functions and the combination would have yielded nothing more than predictable results of treating cancer synergistically with anti-CCR4 antibody and etoposide. Given that the additive effect for anti-CCR4 antibody and VP16 has not been found to be true synergism or merely due to increased amount of total components, the evidence is not sufficient to overcome the *prima facie* case of obviousness set forth in the rejection of record.

Similarly, the evidence on synergy between anti-CCR4 antibody/methotrexate (MTX) shown in Figure 5 and Example 5 was not found convincing for the same reason as that of anti-CCR4/CPA. The difference between the Group A (negative control) and Group D (anti-CCR4 antibody + MTX) is not greater than the combined difference between Group A and Group B (anti-CCR4 antibody alone) and Group A and Group C (MTX alone). The additive effect was not greater than that of each component alone, thus the results are not significant or sufficient to overcome the *prima facie* case of obviousness set forth in the rejection of record.

The evidence on synergy between anti-CCR4 antibody/G-CSF shown in Figure 6 and Example 6 was not found convincing for the same reason as that of anti-CCR4/eptoposide. Although the additive effect of anti-CCR4 antibody/G-CSF combined therapy was is greater than that of each component alone, it is not clear whether the result is due to true synergy or mere an increase in the total amount of the components administered. Given that the prior art taught that G-CSF activates immune cells, one of ordinary skill in the art would have been motivated to include G-CSF in the therapy for cancer. Therefore, the evidence was not sufficient to overcome the *prima facie* case of obviousness set forth in the rejection of record.

The evidence/argument on synergy on anti-CCR4 antibody/IL-15 and anti-CCR4 antibody/IFN-alpha is not considered because IL-15 and IFN-alpha have been withdrawn from further consideration as a non-elected species of agent. Applicant has not made any argue against withdrawing the species.

In response to Applicant's argument that synergy in the pertinent art is unpredictable (page 10 of Applicant's remarks), it is noted that Applicant is arguing limitation not claimed. The present claims are drawn to a method of treating CCR4-expressing tumor comprising administering an anti-CCR4 antibody and one of the recited agents, *not* a synergistic method. Given that Shitara taught a same or nearly the same anti-CCR4 antibody for treating CCR4-expressing cancer and that Taub taught that well-known anti-cancer agents such as vincristine, cyclophosphamide, etoposide or methotrexate would produce synergism in treating cancer (see column 6, lines 9-26); one of ordinary skill in the art, upon reading the combined teachings of Shitara and

Taub, would have been motivated to include a therapeutic agent such as vincristine, cyclophosphamide, etoposide or methotrexate in the medicament comprising the anti-CCR4 antibody as the active agent for treating cancer for the expected results of synergism (e.g., decreasing dose-limiting side effects).

Furthermore, in response to Applicant's argument that Taub did not teach or suggest combination therapy with anti-CCR4 antibodies, it is noted that the nexus between the two prior art is the common purpose of treating cancer. It would have been obvious to one of ordinary skill in the art to combine one of the agents with anti-CCR4 antibody for the same purpose of treating cancer with no change in their respective functions and the combination would have yielded nothing more than predictable results of treating cancer synergistically with anti-CCR4 antibody and one of the agents.

Applicant's argument has been considered in view but has not been found convincing for the above reasons. Therefore, the rejection of record is hereby maintained as it applies to amended claims.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 5-6 and 27-41 stand *provisionally* rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 54, 57-70, 74-75 and 81-84 of copending application, USSN 11/969,555 in view of Shitara et al. (US 2003/0175273 A1) and Taub (U.S. Patent 6,762,174 B1).

Applicant's request to hold this rejection in abeyance until allowable subject matter has been identified is acknowledged. However, this rejection is maintained for reasons of record. The rejection of record can be located in the previous Office Action, mailed 07/22/2009.

Conclusion

7. No claim is allowed.

8. Applicant's request for personal or telephone interview has been acknowledged. However, this Office Action is sufficient to convey the issues remaining in the application at this time.

9. The information disclosure statement (IDS) submitted on 12/22/2009 has been considered by the examiner.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHARON WEN whose telephone number is (571)270-3064. The examiner can normally be reached on Monday-Thursday, 8:30AM-6:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571)272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sharon Wen/
Examiner, Art Unit 1644
April 7, 2010